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Erythropoietin: not just about erythropoiesis

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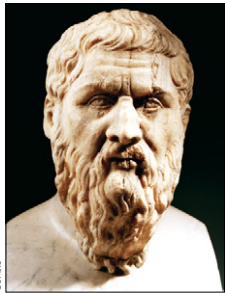
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- 3 Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Shin EK. Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients. *J Am Coll Cardiol* 2010; **55**: 1209–16.



Erythropoietin: not just about erythropoiesis



This online publication has been corrected. The corrected version first appeared at *TheLancet.com* on August 6, 2010

A paper by Sinclair and colleagues¹ in *Blood* challenges, on the basis of observations on cell lines, the concept that erythropoietin has activities unrelated to erythrodifferentiation. Sinclair and colleagues, based at Amgen, have published six papers since 2006 focused on whether the erythropoietin receptor (EPOR) is expressed by tumour cells—a fact that, if true, could have adverse effects for the use of erythropoietin in cancer. They conclude that EPOR is not expressed by many of the cells previously reported to express EPOR and exhibit cytoprotection by erythropoietin, and question the entire concept that erythropoietin is active on non-haemopoietic cells.

Although sometimes data from one laboratory are not replicated in another, many investigators have reported trophic or antiapoptotic effects of erythropoietin on many cells, including those that Sinclair and colleagues report in tabular form without presenting their original data. In fact, over the past 10 years, multiple investigators have shown that erythropoietin is tissue-protective, anti-inflammatory, and promotes neurogenesis and angiogenesis.

The observation that erythropoietin is neuroprotective *in vivo*² ignited substantial interest in its roles and possible therapeutic use in various diseases. Searching for “erythropoietin AND protect*”, PubMed gives 863 hits of which we identified 346 research papers reporting a protective or reparative action, and only ten a lack of extra-haemopoietic effects.

Having no data to compare with previous studies, it is difficult to understand whether “inconsistent,

irreproducible and at best modest (10–20%) effects”¹ refers to the inconsistency of the effect or to Sinclair and colleagues’ experimental technique.

Sinclair and colleagues expand their conclusions further by stating that *in vivo* studies of erythropoietin in animal models of damage are faulty and that they “do not believe [that] clinical studies examining an alleged ‘direct’ effect of ESAs [erythropoiesis-stimulating agents] on heart or brain function or repair are well founded”.¹ The term “alleged” is a hyperbole when referring to the tissue-protective actions of erythropoietin that, independently of the receptors implicated, are supported by hundreds of studies, two meta-analyses,^{3,4} and some clinical trials, although we agree that caution should be used because of potential side-effects.⁵

Cratylus, discussing with Plato, stated that names express the essence of the thing. This is hardly the case for cytokines: look at tumour necrosis factor or interleukin 1. Although, from a pharmaceutical perspective, it would be convenient if erythropoietin had no activities outside erythropoiesis, this is wishful thinking. The field would be better served by efforts to understand the full spectrum of erythropoietin’s actions.

For the full author list see webappendix. PG has received contract money as principal investigator and travel money for meetings from Warren Pharmaceuticals; contract money as principal investigator, travel money, and honoraria from Lundbeck A/S and Amgen; and honoraria from Janssen-Cilag. MB has received contract money as principal investigator from Lundbeck A/S and Amgen. RB has received institutional grants for research from Warren Pharma. BK declares that he has no conflicts of interest.

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Brighton & Sussex Medical School, Falmer BN1 9RY, UK (PG); UMR 6232 CI-NAPS, CERVOxy team, Université de Caen Basse-Normandie, CNRS, CEA, Caen, France (MB); Carlo Besta Neurological Institute, Milan, Italy (RB); and Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden (KB)

- 1 Sinclair AM, Coxon A, McCaffery I, et al. Functional erythropoietin receptor is undetectable in endothelial, cardiac, neuronal, and renal cells. *Blood* 2010; published online Feb 2. DOI:10.1182/blood-2009-10-248666.
- 2 Brines ML, Ghezzi P, Keenan S, et al. Erythropoietin crosses the blood-brain barrier to protect against experimental brain injury. *Proc Natl Acad Sci USA* 2000; **97**: 10526–31.
- 3 Jerndal M, Forsberg K, Sena ES, et al. A systematic review and meta-analysis of erythropoietin in experimental stroke. *J Cereb Blood Flow Metab* 2010; **30**: 961–68.
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Department of Error

UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet* 2002; **359**: 1291–300—In this Article, the authorship line should have read: “W S Atkin, C F Cook, J Cuzick, R Edwards, J M A Northover, J Wardle, for the UK Flexible Sigmoidoscopy Screening Trial Investigators”.

Travis RC, Reeves GK, Green J, et al, for the Million Women Study Collaborators. Gene-environment interactions in 7610 women with breast cancer: prospective evidence from the Million Women Study. *Lancet* 2010; **375**: 2143–51—In this Article (June 19), the funding statement in the Summary and Acknowledgments should have included the Institut National du Cancer (France). Additionally, the affiliation details for Prof M Lathrop should have included Fondation Jean Dausset, Centre d’Etude du Polymorphisme Humain, Paris, France.

Rajaratnam JK, Marcus JR, Flaxman AD, et al. Neonatal, postneonatal, childhood, and under-5 mortality for 187 countries, 1970–2010: a systematic analysis of progress towards Millennium Development Goal 4. *Lancet* 2010; **375**: 1988–2008—In this Article (June 5), the data for Seychelles, Antigua and Barbuda, Dominica, and Marshall Islands in table 1 and table 2 were incorrect. Additionally, the fourth sentence of the sixth paragraph in the Results section should have read “Latin America and the Caribbean have made good progress overall, but Bolivia and Haiti have rates higher than 40 per 1000”. These corrections have been made to the online version as of June 18, 2010. The webappendix of this Article has also been corrected as of this date.

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See [Online](#) for webappendix